LETTERS TO THE EDITOR

- *The British Heart Journal welcomes letters commenting on papers that it has published within the past six months.*
- *All letters must be typed with double spacing and signed by all authors.*
- *No letter should be more than 600 words.*
- *In general, no letter should contain more than six references (also typed with double spacing).*

Immunoglobulin response to intravenous streptokinase in acute myocardial infarction

SIR,—Lynch *et al*'s study (*British Heart Journal* 1991;**66**:139–42) contributes to the growing body of information on the immune response after administration of intravenous streptokinase for acute myocardial infarction. The current focus has been on the length of the period during which important titres of antibodies to and neutralising capacity for streptokinase persist (these do not always correlate precisely[2]). Studies by Lynch *et al*[1] and Jalilal and Morris[3] showed that this period extends at least to 12 months, and further work is awaited to determine the outer limit of this period. During this period streptokinase should not be readministered because of fears of an anaphylactic reaction and also that the drug will be neutralised and hence ineffective.

The current recommendations of the *1990–91 Data Sheet Compendium* are that a second dose of streptokinase should not be given within a period of five days to six months after the first. A recent *Drug and Therapeutics Bulletin* states that this will soon be amended to a 12 month interval.[4] Recent authoritative papers[5,6] have been broader in their recommendations, suggesting that streptokinase and anistreplase should not be readministered within a year, and the latter paper[6] concluded with the assertion that tissue plasminogen activator (alteplase) should be used if repeat thrombolysis is required (no time limit was stated so it presumably extended indefinitely from day 0). A policy of not repeating streptokinase for a year from day 0 has been widely adopted. These conclusions are important because alteplase costs ten times as much as streptokinase.

This policy loses sight of the early window that exists before the development of a significant immune response to streptokinase. This is a worthwhile opportunity given that 9% of patients will reinfarct in the first year after thrombolysis.[7] In a substantial number of these patients reinfarction requiring repeat thrombolysis occurs in the first few days after thrombolysis. In White *et al*'s 1990 study of repeat thrombolysis after myocardial infarction 31 patients were treated for recurrent myocardial infarction after thrombolysis between one and 716 days after initial thrombolysis.[5] The median interval was only five days and 10 of the 31 patients were treated in the first three days. Lynch *et al*'s study shows that antibody titres to streptokinase (IgG) do not rise above baseline until day four, suggesting that a significant immune response (either anaphylactic or neutralising) is unlikely before this. The work of Massel *et al* on neutralising antibody showed a neutralising capacity equivalent to $1{\cdot}5 \times 10^6$ units streptokinase between days five and nine in all their patients[8] (this small study (11 patients) may not have adequately defined the normal range). This again suggests that there is an early opportunity to readminister streptokinase safely and effectively. Indeed though White *et al* recommended that streptokinase should not be readministered within a year they did show that readministration within this period was effective (albeit with an increased incidence of minor side effects).

This evidence suggests that streptokinase can be readministered safely and effectively from 0 to 3 days after the initial event. A further large study of neutralising capacity would be helpful because the most recent study dealt only with antibody response and a previous study of neutralising capacity was small. If this policy is adopted as a refinement of the day 0 to one year policy, which seems to be emerging, it is likely to have an impact on coronary care unit drug bills.

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1 Lynch M, Littler WA, Pentecost BL, Stockley RA. Immunoglobulin response to intravenous streptokinase in acute myocardial infarction. *Br Heart J* 1991;**66**:139–42.
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This letter was shown to the authors and an advsior, who reply as follows:

SIR,—We are grateful to Dr Grant for his comments. We agree, as stated in our final paragraph, that it would be prudent to avoid repeating the dose between three days and at least one year after the initial treatment with streptokinase. After treatment with streptokinase, the antibody titre (IgG, subclass IgG1) virtually disappears, presumably because the antibody combines with the antigen, streptokinase. Subsequently, there is a gradual rise in antibody titre, which does not become significantly higher than baseline titres until day 4. During this time window of 0–3 days, when antibody titres are no higher than pretreatment titres, it is probably as safe and effective to re-administer streptokinase in the event of a repeat infarction as in the case of the initial infarct.

We are continuing to monitor streptokinase antibody titres in this cohort of 20 patients, who have now reached the 18 month time point. Though they are gradually declining, the mean (SD) IgG titres to streptokinase are still significantly raised at two years (86·42 (102·9)) over baseline titres (14·63 (4) ($p < 0{\cdot}025$). Repeat infarction after 72 hours and until at least 18 months after the initial infarct should probably be managed with a non-streptokinase thrombolytic agent until the significance of these antibodies is known.

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SIR,—Dr Grant raises an interesting point about the possible readministration of streptokinase or streptokinase-containing compounds in the first three days after initial administration. Specific antistreptokinase IgG concentrations initially fall and then increase over this time[1] and there may be an early time window when readministration could be safe and effective. However, the time course of the immunological response varies from patient to patient and individual patients may therefore receive ineffective therapy if this approach is adopted.

Readministration of *effective* thrombolytic therapy is important because reocclusion in the first few days is associated with poor clinical outcome and higher mortality. For example, in the TAMI (thrombolysis and angioplasty in myocardial infarction) trials patients who had an initially patent artery that then reoccluded over the first few days had a significant increase in hospital mortality from 4·5% to 11% ($p = 0{\cdot}01$).[2]

Other thrombolytic agents available such as urokinase or alteplase can be used without raising concern about the effectiveness of readministration. It seems prudent, therefore, not to readminister streptokinase or compounds containing streptokinase in the first few days unless evidence emerges that high titres of antistreptokinase IgG or high neutralisation titres do not compromise safety or efficacy.

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1 Lynch M, Littler WA, Pentecost BL, Stockley RA. Immunoglobulin response to intravenous streptokinase in acute myocardial infarction. *Br Heart J* 1991;**66**:139–42.
2 Ohman EM, Califf RM, Topol EJ, Candela R, Abbottsmith C, Ellis S, Sigmon KN, Kereiakes D, George B, Stack R, and the TAMI study group. Consequences of reocclusion after successful reperfusion therapy in acute myocardial infarction. *Circulation* 1990;**82**:781–91.

Myocardial ischaemia and ventricular arrhythmias precipitated by physiological concentrations of adrenaline in patients with coronary artery disease

SIR,—McCance and Forfar (*British Heart Journal* 1991;**66**:316–9) reported the effects of adrenaline on the development of ischaemia and arrhythmia in patients with ischaemic

heart disease.[1] One of their principal findings was that adrenaline produced ischaemia at a lower rate-pressure product than exercise. This raises many important questions about the mechanisms through which catecholamines produce ischaemia and about how such ischaemia can be prevented.

McCance and Forfar postulate that redistribution of coronary flow is the mechanism underlying the greater ischaemic effect of adrenaline, but recent biochemical data suggest an alternative explanation. Adrenaline (released from the adrenal medulla during stress) is a more potent stimulator of the β-2 subtype of adrenoreceptor than noradrenaline (released from the sympathetic nerve endings during exercise). Stimulation of cardiac β-2 adrenoreceptors, like β-1 adrenoreceptors, has positive inotropic and chronotropic effects.[2,3] However, biochemical studies have shown important differences in the linkage of β adrenoreceptor subtypes to cardiac adenylate cyclase, with a higher proportion being linked to β-2 adrenoreceptors than to β-1 adrenoreceptors.[4] Not all adenylate cyclase when activated leads to increased contractility; therefore, adrenaline activation of adenylate cyclase not linked to contraction (possibly linked to metabolic pathways) may lead to a further increase in oxygen consumption. This differential coupling to adenylate cyclase may explain why adrenaline infusions produce greater ischaemia than exercise for a given rate-pressure product.

Whatever the underlying mechanism, this study has important therapeutic implications. By failing to block β-2 adrenoreceptors selective β-1 blockade will be inferior to non-selective β-blockade at antagonising the effects of adrenaline. Additionally selective β-1 blockade may actually lead to an enhancement of the ischaemic and arrhythmogenic effects of adrenaline because β-1 blocker treatment leads to a selective enhancement of the sensitivity of the heart to β-2 adrenoreceptor stimulation.[5-7] This may have enhanced the differences between exercise and adrenaline infusion seen in McCance and Forfar's study since 13/14 patients were taking a β-1 selective blocker (atenolol, metoprolol, and bisoprolol) until a few days before the study. Therefore this study adds further weight to the argument that non-selective β blockade may have advantages over β-1 selective blockade during stress—for example, myocardial infarction.

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1 McCance AJ, Forfar JC. Myocardial ischaemia and ventricular arrhythmias precipitated by physiological concentrations of adrenaline in patients with coronary artery disease. *Br Heart J* 1991;**66**:316–9.
2 Kaumann AJ, Lemoine H. β-2 adrenoreceptor mediated positive inotropic effect of adrenaline in human ventricular myocardium. *Naunyn-Schiedebergs Arch Pharmacol* 1987;**335**: 403–11.
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5 Hall JA, Kaumann AJ, Brown MJ. Selective β-1 adrenoreceptor blockade enhances positive inotropic responses to endogenous catecholamines mediated through β-2 adrenoreceptors in human atrial myocardium. *Circ Res* 1990;**66**:1610–23.
6 Hall JA, Petch MC, Brown MJ. In vivo evidence of cardiac β-2 adrenoreceptor sensitisation due to atenolol treatment. *Circ Res* 1991; **69**:959–64.
7 Ferro A, Hall JA, Brown MJ. Selective potentiation of cardiac β-2 responses caused by β-1 blockade with bisoprolol 1991. *Clin Sci* 1991;**81**(suppl 25):16.

This letter was shown to the authors who reply as follows:

SIR,—We thank Hall and Ferro for their interesting comments on our paper. The mechanism of our observation that adrenaline produced ischaemia at a lower rate-pressure product than exercise must remain speculative, but we agree that the mechanism proposed by Hall and Ferro is also consistent with our data.

It is interesting to consider the ideal properties for a β blocker in the setting of acute myocardial infarction. The beta-1 selective agent atenolol was shown in ISIS-1[1] to reduce mortality when used early in acute myocardial infarction, a benefit largely due to a decrease in cardiac rupture. No other β blocker has been shown to decrease mortality when given acutely. But both propranolol[2] and metoprolol[3] have been shown to reduce ventricular fibrillation in acute myocardial infarction. In animal studies timolol, pindolol, propranolol, metoprolol, and labetalol all increased the ventricular fibrillation threshold to a similar extent.[4]

Adrenaline is unlikely to be of direct relevance in causing late mortality after acute myocardial infarction but the question of which β blocker to use orally *after* acute myocardial infarction is as important as the question of which β blocker to use acutely. Propranolol, timolol, and metoprolol are all reported to reduce mortality and particularly sudden death after acute infarction.[5] The mechanisms of benefit may be many and are probably different from those when β blockers are used acutely.[6] It may be that here lipid solubility is more important than β-1 selectivity. An overview of the long-term β blocker trials has not suggested any difference between the β-1 selective and non-selective β blockers,[7] though it seems that β blockers that do not have partial agonist activity may be more effective than those that do. There are insufficient data to be certain whether lipid solubility is important in this respect but all the drugs known to be efficacious are lipid soluble. Given the uncertainty about the importance of the ancillary properties of β blockers it seems reasonable to suggest that only β blockers with proven effects should be used for postinfarction prophylaxis[5] and, despite the theoretical advantages of non-selective β blockade advanced by Hall and Ferro, the same is probably true of the use of intravenous β blockade in acute infarction. Thus we believe that, in the absence of proof of the relative benefits of non-selective and selective β blockers, atenolol and possibly metoprolol should remain for the present the first line intravenous β blockers in acute myocardial infarction.

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1 ISIS-1 (First International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous atenolol among 16,027 cases of suspected acute myocardial infarction. *Lancet* 1986;ii:57–66.
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Cyclosporin treatment and nitric oxide release in human coronary arteries

SIR,—We read with interest the report by Dr O'Neil and colleagues (*British Heart Journal* 1991;**66**:212–6) of the lack of effect of cyclosporin on nitric oxide release in human coronary arteries.[1] The data they presented are most valuable because they were obtained from human studies. However, we feel that the conclusion of the paper should be re-examined in the light of their results.

To assess the effect of cyclosporin in vitro, O'Neil *et al* applied the protocol that we have previously described.[2] After three hours of incubation with cyclosporin, the maximal relaxation (mean (SEM)) to substance P was reduced from 76·6 (7·4)% in control coronary artery rings to 63·0 (11·5)% and 62·2 (11·1)% in rings pretreated with cyclosporin 1000 and 2000 ng/ml, respectively. This difference was not statistically significant. However, at lower concentrations (10^{-10} and 10^{-9} mol/l) of substance P, the relaxant responses were significantly reduced in coronary artery rings incubated with cyclosporin compared with control rings (shown by O'Neil *et al* in fig 1). Substance P is known as an endothelium-dependent vasodilator[3] and has already been used by O'Neil *et al* to test the ability of the coronary circulation to release nitric oxide in vitro in humans.[4] As with other human vascular diseases,[5,6] the mechanisms for relaxation of the underlying vascular smooth muscle in response to nitrovasodilators were not affected by cyclosporin (shown by O'Neil *et al* in fig 2). We therefore cannot see any other interpretation than the one suggesting that nitric oxide release is indeed impaired in rings incubated with cyclosporin when tested with low concentrations (10^{-10} and 10^{-9} mol/l) of substance P. Usually when they find no statistical difference between the maximal responses of the rings workers calculate the dose of agonist eliciting 50% of the full response (EC_{50}). This universally accepted method allows the detection of any shift of the dose-response curves. Inspection of fig 1 indicates that there is indeed a rightward shift of the dose-response curves obtained from rings treated with cyclosporin in vitro.

O'Neil *et al* found no significant correlation between the in vivo and in vitro coronary vasodilatory responses to substance P with either blood concentration of cyclosporin (fig